

71486/PCT

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date  
24 July 2003 (24.07.2003)

PCT

(10) International Publication Number  
**WO 2003/059281 A3**

(51) International Patent Classification<sup>7</sup>: **C07K 14/00**, C12N 5/00, A61K 38/00

(74) Agent: SILVA, Robin, M.; Flehr Hohbach Test Albritton & Herbert LLP, 4 Embarcadero Center, Suite 3400, San Francisco, CA 94111-4187 (US).

(21) International Application Number:

PCT/US2003/000393

(22) International Filing Date: 6 January 2003 (06.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/345,805 4 January 2002 (04.01.2002) US  
60/373,453 17 April 2002 (17.04.2002) US  
60/374,035 19 April 2002 (19.04.2002) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US	60/345,805 (CIP)
Filed on	4 January 2002 (04.01.2002)
US	60/373,453 (CIP)
Filed on	17 April 2002 (17.04.2002)

(71) Applicant (for all designated States except US): XEN-COR [US/US]; 111 West Lemon Avenue, Monrovia, CA 91016 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): DESJARLAIS, John, R. [US/US]; 2096 Crary Street, Pasadena, CA 91104 (US). HUBERT, Rene, S. [CA/US]; 1644 Occidental Boulevard, Los Angeles, CA 90026 (US). YAZAL, Jamal, El [BE/US]; 6731 Florence Place, Alta Loma, CA 91701 (US). MARSHALL, Shannon, Alicia [US/US]; 825 Lincoln Way, #106, San Francisco, CA 94122 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:  
2 June 2005

(15) Information about Correction:

Previous Correction:

see PCT Gazette No. 17/2004 of 22 April 2004, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/059281 A3

(54) Title: NOVEL VARIANTS OF RANKL PROTEIN

(57) Abstract: The present invention relates to novel, soluble, recombinant variants RANKL (Receptor Activator of Nuclear Factor -kB ligand) proteins, which may be expressed solubly in *E. coli*, variants that act as RANKL antagonists, and methods for generating the same.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/00393

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C07K 14/00; C12N 5/00; A61K 38/00  
US CL : 530/350; 435/69.1; 514/2

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350; 435/69.1; 514/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
WEST, keywords RANKL, trimer, variant, osteoprotegerin

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,242,213 B1 (ANDERSON) 05 June 2001 (05.06.2001), column 3, lines 40-66, column 4, lines 35-56; column 23-64; column 6, line 59-column 7, line 6; column 7, lines 5-27 and lines 41-47; column 10, lines 5-46; column 11, line 5-column 14, line 66; column 15, line 28-column 16, line and column 27, lines 41-47.	1,2,8,11-16,21,23-26, 31-40

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

21 January 2005 (21.01.2005)

Date of mailing of the international search report

17 MAR 2005

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Faxsimile No. (703) 305-3230

Authorized officer

Regina M. DeBerry

Telephone No. 571-272-1600

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/00393

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claim Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claim Nos.: 6,7,9,10 and 17-20 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
No computer readable form of the sequence listing was furnished.
  
3.  Claim Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## PATENT COOPERATION TREATY

PCT

REC'D 13 MAY 2005

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

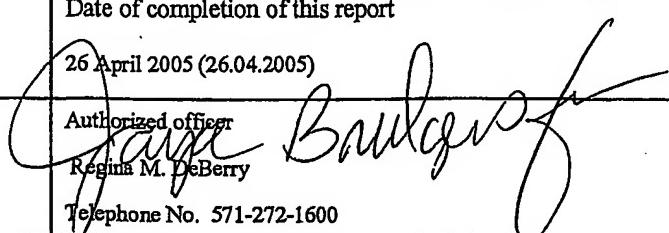
Applicant's or agent's file reference PP71486/RMS	FOR FURTHER ACTION      See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPRA/416)	
International application No. PCT/US03/00393	International filing date (day/month/year) 06 January 2003 (06.01.2003)	Priority date (day/month/year) 04 January 2002 (04.01.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07K 14/00; C12N 5/00; A61K 38/00 and US Cl.: 530/350; 435/69.1; 514/2		
Applicant XENCOR		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
- This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of \_\_\_ sheets.

3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of report with regard to novelty, inventive step and industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand 04 August 2003 (04.08.2003)	Date of completion of this report 26 April 2005 (26.04.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/ US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	 Authorized officer Regina M. DeBerry Telephone No. 571-272-1600

**I. Basis of the report****1. With regard to the elements of the international application:\***

- the international application as originally filed.
- the description:  
pages 1-42 as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_.
- the claims:  
pages 43-46, as originally filed  
pages NONE, as amended (together with any statement) under Article 19  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_.
- the drawings:  
pages 1-30, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_.
- the sequence listing part of the description:  
pages none, as originally filed  
pages NONE, filed with the demand  
pages NONE, filed with the letter of \_\_\_\_\_.

**2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.**

These elements were available or furnished to this Authority in the following language \_\_\_\_\_ which is:

- the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).  
 the language of publication of the international application (under Rule 48.3(b)).  
 the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

**3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:**

- contained in the international application in printed form.  
 filed together with the international application in computer readable form.  
 furnished subsequently to this Authority in written form.  
 furnished subsequently to this Authority in computer readable form.  
 The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
 The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

**4.  The amendments have resulted in the cancellation of:**

- the description, pages none  
 the claims, Nos. none  
 the drawings, sheets/fig none

**5.**  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).\*\*

\* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

\*\* Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US03/00393

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- the entire international application,  
 claims Nos. 6,7,9,10 and 17-20

because:

- the said international application, or the said claim Nos. \_\_\_\_\_ relate to the following subject matter which does not require international preliminary examination (*specify*):

- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. \_\_\_\_\_ are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. \_\_\_\_\_ are so inadequately supported by the description that no meaningful opinion could be formed.  
 no international search report has been established for said claims Nos. 6,7,9,10 and 17-20

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- the written form has not been furnished or does not comply with the standard.  
 the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. STATEMENT**

Novelty (N)	Claims <u>3-5,22 and 27-30</u>	YES
	Claims <u>1,2,8,11-16,21,23-26,31-40</u>	NO
Inventive Step (IS)	Claims <u>3-5,22,27-30</u>	YES
	Claims <u>1,2,8,11-16,21,23-26,31-40</u>	NO
Industrial Applicability (IA)	Claims <u>1-5,8 11-16,21-40</u>	YES
	Claims <u>NONE</u>	NO

**2. CITATIONS AND EXPLANATIONS**

Claims 1, 2, 8, 11-16, 21, 23-26, 31-40 novelty under PCT Article 33(2) as being anticipated by Anderson, US 6,242,213 B1. Anderson teaches RANKL isolated polypeptides and analogues, which may be modified by forming covalent conjugates with chemical moieties. Anderson teaches cross-linking and covalently binding RANKL to various agents (column 3, lines 40-67). Anderson teaches RANKL polypeptides, which have the activity to bind RANK and/or inhibit RANKL induce signaling. Anderson teaches fragments of the extracellular domain of RANKL (column 4, lines 35-56). Anderson teaches fusion proteins of RANKL comprising the immunoglobulin of IgG (column 5, lines 23-40). Anderson teaches that if the fusion protein is made with both heavy and light chains of an antibody, it is possible to form a protein oligomer with as many as four RANKL regions (column 5, lines 39-41). Anderson teaches RANKL proteins comprising oligomerizing peptides such as a leucine zipper (column 5, lines 42-64). Anderson teaches ways to form dimers, trimers and tetramers (column 6, line 59-column 7, line 6). Anderson teaches soluble forms of oligomeric RANKL comprising a trimer-former leucine zipper (column 27, lines 41-47). Anderson teaches RANKL with or without native glycosylation patterns (column 7, lines 5-27) and cysteine residues that can be deleted or replaced with different amino acids (column 7, lines 41-50). Anderson teaches methods of substituting amino acids in the polar region and regions of hydrophobicity. Anderson teaches methods of identifying RANKL agonists and antagonists (column 10, lines 5-46), linkers (column 11, lines 1-5) and recombinant methods of making RANKL (column 11, line 5-column 14, line 66). Anderson teaches pharmaceutical compositions of RANKL (column 15, line 28-column 16, line 15).

Claims 3-5, 22, 27-30 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the instant invention of specific mutations made in the RANKL extracellular domain.

**----- NEW CITATIONS -----**

NONE